Therapeutic Products Programme

GUIDELINE

STEREOCHEMICAL ISSUES IN CHIRAL DRUG DEVELOPMENT

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Therapeutic Products Programme

GUIDELINE[1]

STEREOCHEMICAL ISSUES IN CHIRAL DRUG DEVELOPMENT

1. INTRODUCTION

1.1 PURPOSE

This document is intended to provide sponsors of New Drug Submissions (NDS's) and Abbreviated New Drug Submissions (ANDS's) with guidance on issues specific to chiral pharmaceuticals that should be addressed during drug development. It complements the existing Directorate's guidelines on *Chemistry and Manufacturing: New Drugs* and *Toxicologic Evaluation*.

The Therapeutic Products Directorate recognizes that this document cannot cover every possible situation and each submission will be considered and judged on its own merits.

Alternate approaches to the principles and practices described in this guideline may be acceptable provided they are supported by adequate scientific justification. However, submission sponsors are encouraged to discuss, in advance, significant variations with the Directorate to avoid rejection or withdrawal of the submission.

1.2 BACKGROUND

It should be emphasized that the scientific and regulatory principles that underlie chiral drugs are not fundamentally different from those of non-chiral drugs; however, it has been recognized for some time that the chirality of drugs poses unique problems. Progress in enantioselective synthesis and enantioselective separation, and better understanding of the *in vivo* behaviour of enantiomers now permit the stereochemical issues of chiral drug development to be addressed from a regulatory perspective.

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1 Guidelines provide assistance to external clients on **how** they may comply with statutory and regulatory requirements of the *Food and Drugs Act, Food and Drug Regulations, Controlled Drug and Substances Act, Narcotic Control Regulations, or Medical Devices Regulations*, as well as interpretations of section(s) thereof. Guidelines also provide specific review and compliance approaches to TPP staff, helping to ensure that the Programme's mandate is implemented in an effective, fair, and consistent manner.

This and other Guidance Documents are available on the Therapeutic Products Programme (TPP) Website (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). Guidelines listed on the Directorate's *Guidelines Order Form* are available in printed form only, through the Canadian Government Publishing Centre (CGPC). The *Order Form* is available on the TP Website under "Forms" or from the CGPC (Tel: 819-956-4800; Fax: 819-994-1498; Internet: http://publications.pwgsc.gc.ca).

A glossary of terms related to stereochemistry may be found in Appendix 1. With respect to nomenclature, chemical names should be expressed according to the International Union of Pure and Applied Chemistry (IUPAC) or Chemical Abstract (CAS) rules.

Stereoisomers are compounds made up of the same atoms bonded in the same sequence but having different orientations in space. The term stereoisomer encompasses diastereoisomers (including cis-trans isomers) and enantiomers. Diastereoisomers are chemically distinct and often pharmacologically different compounds, and can generally be separated by achiral analytical methods. Therefore, they should be developed separately, not as a mixture, as drugs unless *in vivo* interconversion of the isomers occurs, or the mixture fortuitously represents a reasonable fixed dose combination. This class of stereoisomers is not the focus of this document.

Enantiomers are stereoisomers whose mirror images cannot be superimposed. Enantiomers have identical physical and chemical properties except that they rotate the plane of polarized light in opposite directions and behave differently in a chiral environment. Thus, they interact at different rates with other chiral compounds including many biological macromolecules.

Mixtures of equimolar amounts of enantiomers are called racemates. They may exist as racemic mixtures (conglomerates) or racemic compounds (true racemates). In the solid state, the physical properties such as melting points, solubilities and heats of fusion of the racemates may differ from those of the individual enantiomers.

Many drugs are marketed as racemates. There are numerous examples in the literature where the enantiomers in a racemate differ substantially with respect to their pharmacokinetics, pharmacodynamics, toxicity, protein binding, etc. With some drugs, only one of the enantiomers is mostly responsible for a given pharmacological activity. The other enantiomer may be less active, inactive, toxic, or may give rise to an entirely different pharmacological response. Interactions between enantiomers have been also described. Consequently, enantiomers should be recognized as distinct substances.

1.3 SCOPE

This guideline specifically deals with issues related to the development of enantiomers and their mixtures. It applies to pharmaceutical drugs, including synthetic drugs, semi-synthetic drugs, and drugs produced from fermentation or derived from natural sources. It does not apply to biologics or radiopharmaceuticals.

1.4 PREAMBLE

The decision whether to develop a single enantiomer, racemate, or non-racemic mixture (enantiomeric mixture other than racemate) rests with the sponsor and should be based on scientific data relating to quality, safety and efficacy and ultimately to the risk/benefit assessment of the drug under the proposed conditions of use. Cases where the development of a racemate may be justified include, but are not limited to, the following:

a) The enantiomers are configurationally unstable *in vitro* or undergo racemization *in vivo*.
b) The enantiomers have similar pharmacokinetic, pharmacodynamic and toxicological properties.
c) It is not technically feasible to separate the enantiomers in sufficient quantity and/or with sufficient quality.

The cases where development of a non-racemic mixture may be justified include those where a specific enantiomeric ratio is expected to improve the therapeutic profile.

The requirements for drug submissions concerning chiral drugs are outlined in the sections that follow. It is emphasized that these requirements are not all encompassing and depending on the drug, may vary as to specifics. If it is believed that a particular drug requires more definitive guidance, the sponsor is encouraged to discuss the issues with the Directorate in advance.

Enantioselective assays should be developed and validated at an early stage of drug development, and used wherever relevant unless it has been clearly demonstrated that a non-enantioselective assay provides results equivalent to those obtained with the enantioselective assay. A list of analytical methods for chiral drugs may be found in Appendix 2.

2. CHEMISTRY AND MANUFACTURING

The requirements of the Directorate's guideline on *Chemistry and Manufacturing: New Drugs* are applicable to both chiral and non-chiral drugs. This section discusses additional requirements that are specific to chiral drugs.

2.1 SINGLE ENANTIOMER[2]

2.1.1 Drug Substance

A full description of the manufacturing process used to obtain the individual enantiomer should be given. The identity and enantiomeric purity of chiral starting materials and chiral reagents should be established. In-process testing for identity and purity should be enantioselective for key intermediates in which chirality has been introduced. Whenever possible, absolute configuration should be determined as part of structural elucidation studies.

Specifications for the drug substance should include enantioselective tests for identity and purity. Optical rotation may be used for both, but in addition, enantiomeric purity should be established by a second validated enantioselective analytical procedure. Reference standards should be available for the enantiomer and the antipode, and both should be of high enantiomeric purity. A limit should be specified for the antipode and this limit should be consistent with the levels found in batches used in preclinical and clinical studies.

The stability of the drug substance towards racemization under stress conditions and on long-term storage should be investigated.

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2 Diastereoisomers are potential impurities in the drug substance and the drug product, based on a single enantiomer containing two or more chiral carbons. Since these impurities are chemically distinct from the enantiomer, they should be investigated and limited as drug substance/drug product impurities in accordance with the Directorate's guideline *Chemistry and Manufacturing: New Drugs*.

2.1.2 Drug Product

The enantiomeric purity of the drug substance in the finished product prior to and during the stability studies conducted to determine shelf-life should be investigated using a validated enantioselective method. A test for enantiomeric purity should be incorporated into the drug Product specifications if results of these investigations warrant.

2.2 RACEMATE

The physicochemical properties, including the nature of the racemate, i.e., whether a racemic compound (true racemate) or racemic mixture (conglomerate), should be investigated. A test for the identity of the racemate should be developed to ensure that spontaneous resolution has not occurred during the purification of the bulk drug. Also, when technically feasible, basic physicochemical information on the individual enantiomers should be provided. Typically, this may include information on melting point, optical rotation, crystal form, and stability towards racemization.

2.3 NON-RACEMIC MIXTURE

2.3.1 Drug Substance

Two different types of mixtures are considered.

a) An enantiomerically enriched drug substance resulting from incomplete resolution or partial enantioselective synthesis.
b) A mixture of enantiomers in specified proportions.

Enantioselective tests for identity and composition are required in the specifications. Optical rotation may be suitable for identity but a more specific and sensitive method is required for the quantitative determination of the enantiomers. Limits should be set for each component based on the composition of the batches used in preclinical and clinical studies. Pure reference standards should be prepared for each component. The stability of the mixture under stress conditions and on long-term storage under ambient conditions should be investigated.

2.3.2 Drug Product

A test with limits on the composition of the mixture is required in the finished product specifications and the relative proportions of the components should be monitored in the shelf-life stability studies.

3. PRECLINICAL AND CLINICAL

3.1 SINGLE ENANTIOMER

In addition to the same documentation as required for any non-marketed new active substance, information on the following should be provided:

The *in vivo* stability of the enantiomer must be established. If the antipode is formed *in vivo*, it should be considered to be a metabolite, and addressed as such during the drug development process. The metabolism and disposition of the enantiomer should be followed using enantioselective methods in each species used in preclinical studies, and in the Phase I studies in humans. If it is established that racemization or inversion does not occur, enantioselective methods may not be needed in all subsequent studies.

3.2 RACEMATE

In addition to the same documentation as required for any non-marketed racemate, information on the following should be provided:

a) Primary and secondary pharmacodynamic effects of each enantiomer in animals and *in vitro* systems with regard to potency, specificity, maximum effect, etc., where appropriate.
b) Pharmacokinetic studies in animals and in humans using enantioselective assays to validate the results of acute and multiple-dose toxicity studies performed with the racemate. Pharmacokinetic studies should be performed in animals with the same doses/routes/species as the toxicological studies and in humans at the proposed therapeutic doses, at steady state where applicable. Validated enantioselective analytical techniques should also be used in subsequent studies.

3.3 SWITCH FROM A RACEMATE TO AN ENANTIOMER

The documentation required for a single enantiomer of a marketed racemate is the same as that for any new active substance. However, many of the studies already performed with the racemate may not have to be repeated with the selected enantiomer, if adequate "bridging studies" have been performed. The purpose of the bridging studies is to validate the relevancy of the studies performed with the racemate, and therefore, the nature of the studies must be determined on a case by case basis. Examples of bridging studies are:

a) Comparison of the acute toxicity, the pharmacodynamic activity and the pharmacokinetics of the selected enantiomer and racemate.
b) Preclinical toxicology bridging studies could consist of repeat dose studies, the duration of which would depend upon the proposed duration of use in man. In general, these studies should not be shorter than three months, with exceptions (e.g., single dose drugs such as neuromuscular relaxants). In addition, the reproductive toxicology segment II study should be repeated in the most sensitive and relevant species, using the single enantiomer.

4. BIOEQUIVALENCE REQUIREMENTS FOR ORAL SOLID DOSAGE FORMS

The requirements outlined below apply to subsequent-market entries of oral solid dosage forms and variations of existing dosage forms that are to be evaluated based on bioequivalence studies.

Comparative bioavailability of products containing a single enantiomer or a mixture of enantiomers should be assessed against an acceptable Canadian Reference Product as defined in section C.08.002.1 of the *Food and Drug Regulations* (see the Directorate's guidelines *Conduct and Analysis of Bioavailability and Bioequivalence Studies- Parts A and B*). Comparisons should be made between pharmaceutically equivalent products that meet standards for enantiomeric purity/composition acceptable to the Directorate.

In the case of a mixture of enantiomers, a potential *in vivo* difference in enantiomeric ratio between the reference product and the subsequent-market entry product is the concern.

In general, for conventional oral solid dosage forms, for which the rate of release of the drug from the formulation does not influence the relative concentration ratio of the enantiomers, the parameters to be determined and the standards to be met will be the same as those specified in the above mentioned guidelines and will be based on total drug. However, for drugs for which it is known that the rate of release and/or absorption into the systemic circulation affects the *in vivo* enantiomeric ratio (e.g., drugs with enantioselective non-linear first pass metabolism), these requirements must be met on each enantiomer.

The rate of input (release and/or absorption) and in turn, the ratio of individual enantiomers in the systemic circulation is more likely to be different for modified-release dosage forms than conventional dosage forms. Therefore, in the case of modified-release formulations, comparative bioavailability requirements will have to be met for both enantiomers unless it can be clearly demonstrated that they possess similar pharmacokinetic or pharmacological properties.

Enantioselective assay is required for conventional or modified-release products containing only a single enantiomer where it is known that inversion of the enantiomer occurs *in vivo*.

APPENDIX 1 - GLOSSARY

ABSOLUTE CONFIGURATION (or Absolute Stereochemistry) - The specific three-dimensional arrangement of substituents around a chiral element.

ANTIPODE - The mirror image isomer of a chiral molecule. A pair of enantiomers are known as optical antipodes.

CAHN-INGOLD-PRELOG CONVENTION - The assignment of configuration about a chiral atom as "R" or "S" by designation of the sequence according to a set of rules.

CHIRALITY - The property of nonsuperimposability of a molecule on its mirror image. A molecule that contains just one carbon atom (called chiral carbon) connected to four different groups is chiral. Chirality in a molecule could be also induced, for example, by the presence of other quadrivalent chiral atoms, restricted rotation about single bonds, or by helicity.

CHIRAL INVERSION - Conversion of one enantiomer into its mirror image.

CONFIGURATIONS - If two different three-dimensional arrangements in space of the atoms in a molecule are not interconvertible by free rotation about bonds, they are called configurations.

CONFORMERS - If two different three-dimensional arrangements in space of the atoms in a molecule are interconvertible merely by free rotation about bonds, they are called conformers.

DIASTEREOISOMERS - IUPAC defines diastereoisomers as "Stereoisomers that are not enantiomeric". Diastereoisomers may be chiral or achiral. However, the term diastereoisomers is used currently by many scientific publications to denote exclusively diastereoisomers that are chiral.

DISTOMER - Refers to the enantiomer with lower pharmacological affinity or activity. Note: A "distomer" for one particular activity can be the "eutomer" for another activity

ENANTIOMERS - Stereoisomers whose mirror images cannot be superimposed.

ENANTIOMERIC PURITY/ENANTIOMERIC EXCESS - The percentage of the enantiomer in excess of its antipode. A drug substance containing 99% of an enantiomer and 1% of the antipode has an enantiomeric purity of 98%.

ENANTIOSELECTIVITY - Characteristic of a process whereby one enantiomer is favoured exclusively or predominantly over the other. In pharmacological terms, the extent to which a biological structure, i.e., an enzyme or any other macromolecular structure (e.g., antibody or receptor) exhibits affinity towards one enantiomer over the other.

ENANTIOSELECTIVE ASSAY - Analytical method capable of separating and quantifying enantiomers.

ENANTIOSELECTIVE SYNTHESIS - Any reaction in which one enantiomer is formed predominantly or exclusively.

EPIMERS - Two diastereoisomers that have a different configuration at only one chiral centre.

EPIMERIZATION - The change of configuration at a chiral centre in a molecule containing two or more chiral centres.

EUDISMIC RATIO - The pharmacological potency ratio of two enantiomers is called the eudismic ratio, and its logarithm, the eudismic index (EI).

EUTOMER - Refers to the enantiomer with higher pharmacological affinity or activity.

ISOMERS - Compounds that have identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space.

cis-trans ISOMERS (Geometric Isomers) - Stereoisomers that differ only in the arrangement of atoms relative to a specified plane in cases where these atoms are, or are considered as if they were parts of a rigid structure, e.g., a ring or a double bond.

MESO-COMPOUND - A compound containing two or more chiral centres, whose mirror images are superimposable because the molecule as a whole is symmetric.

OPTICAL ROTATION - The change of direction of the plane of polarized light to either the right or to the left as it passes through a molecule.

RACEMATE - A mixture of equimolar amounts of enantiomers.

RACEMIC COMPOUND - A homogeneous solid phase composed of equimolar amounts of enantiomeric molecules.

RACEMIC MIXTURE - A mixture of equimolar amounts of enantiomeric molecules present as separate solid phases.

RACEMIZATION - Conversion of an enantiomer to its racemate.

STEREOISOMERS - Isomers that differ in the arrangement of atoms in space.

STEREOSELECTIVITY - Characteristic of a process whereby one of a set of stereoisomers is favoured predominantly or exclusively over the others.

STEREOSPECIFICITY - Characteristic of a process whereby stereoisomers of a molecule induce stereoisomerically different effects. All stereospecific processes are stereoselective but the converse is not true.

In a stereoselective synthesis, one of a set of isomers is predominantly or exclusively formed whereas in a stereospecific synthesis, one isomer leads to one product while another isomer leads to the opposite product.

APPENDIX 2 - ANALYTICAL METHODS FOR CHIRAL DRUGS

Physico-chemical methods that can be used to provide information about chiral drugs are listed below. This is by no means an exhaustive list, and any validated method that is demonstrated to be useful will be considered.

CHIRAL HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC) - Chiral HPLC may be used to separate mixtures of enantiomers directly without forming diastereoisomeric derivatives. Separations can be effected through the use of chiral stationary phases, or chiral mobile phase additives in conjunction with regular (achiral) columns.

CHIRAL GAS CHROMATOGRAPHY - Stationary phases modified with chiral supports are available for the separation of enantiomers.

MELTING POINT - The melting points may be used in distinguishing individual enantiomers from the racemate.

NUCLEAR MAGNETIC RESONANCE (NMR) - NMR is a powerful tool for the determination of enantiomeric purity or enantiomeric composition. This is accomplished by making the NMR signals for the protons of the enantiomers non-equivalent by the use of chiral lanthanide shift reagents, chiral solvating agents or chiral derivatizing agents.

OPTICAL ROTATION - This method can be used to distinguish between enantiomers because they rotate the plane of polarized light in opposite directions but in equal amounts.

OPTICAL ROTATORY DISPERSION (ORD) AND CIRCULAR DICHROISM (CD) - ORD measures the change of specific rotation of an optically active compound with the wavelength of the light used. CD measures the differential absorption of left and right circularly polarized light by an optically active compound. These chiroptical methods can be used to identify and/ or quantitate enantiomers.

X-RAY CRYSTALLOGRAPHY - X-Ray crystallography in the solid state could be used to determine the absolute configuration of molecules and to distinguish conglomerates from racemic compounds.

Health Canada Santé Canada

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July 9, 1998 / Le 9 juillet 1998

98-021711

To: Associations

Subject: Stereochemical Issues in Chiral Drug Development

Aux : Associations

Objet : Développement des médicaments chiraux questions reliées à la stéréo-isomérie

In April 1994 the draft *Guideline on the Development of Stereoisomeric Drugs* (dated December 1993) was circulated to clients and stakeholders for comment. The guideline was intended to provide drug submission sponsors with guidance on issues, specific to chiral pharmaceuticals, that should be addressed during drug development.

En avril 1994, nous avons fait circuler le projet *Guideline on the Development of Stereoisomeric Drugs* (Directive sur le

En réponse aux commentaires internes et externes reçus,

le document, maintenant intitulé *Développement des*

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développement de médicaments stéréoisomériques) (en date de décembre 1993) chez nos clients et partenaires pour obtenir leurs commentaires. La directive avait pour but de préciser aux promoteurs de drogues nouvelles les aspects ayant trait aux produits pharmaceutiques chiraux qu'ils doivent considérer tout particulièrement dans leurs travaux de développement de médicaments. In response to internal and external comments received, extensive revisions have been made to the document, now entitled *Stereochemical Issues in Chiral Drug Development* (attached) to more accurately reflect the focus of the guideline. Revisions were necessary to make for a clearer, more consistent document, and to provide a greater degree of guidance on specific issues. Changes include:

médicaments chiraux questions reliées à la stéréo-isomérie (ci-joint), a été entièrement révisé pour préciser davantage l'objet de la directive. La révision a été nécessaire pour rendre le document plus clair et plus logique et pour donner des indications plus précises sur certains points. Voici les changements qui ont été apportés :

- re-formatting and rewording of the document to improve readability;

- Nouvelle présentation et reformulation pour rendre le document plus intelligible;

- limiting explicitly the scope of the guideline to enantiomers, thereby eliminating a source of ambiguity;

- restriction explicite de l'application de la directive aux énantiomères, de façon à éliminer une source

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- expanding/revising the Glossary; and

- restricting discussion to issues unique to chiral drugs as opposed to those common to other drugs, and covered in existing Directorate guidelines.

- restriction de la discussion aux sujets intéressant spécifiquement les médicaments chiraux plutôt qu'à ceux communs aux autres médicaments qu'on peut retrouver dans d'autres directives de la Direction;- under Preclinical and Clinical:

  - for single enantiomers, introducing a statement that describes the need to use an enantioselective assay to monitor the metabolism and disposition of the enantiomer in preclinical and Phase I studies; and

  - for racemates, expanding the requirement to use enantioselective analytical methods in the pharmacokinetic studies conducted;

d'ambiguïté;

- expansion et révision du glossaire; et

- sous Études précliniques et cliniques:

  - pour un seul énantiomère, indication de la nécessité d'utiliser un essai énantiosélectif pour contrôler le métabolisme et l'élimination de l'énantiomère dans les études précliniques et les études de phase I;

  - pour un racémate, addition de l'exigence d'utiliser des méthodes d'analyse énantiosélective dans les études pharmacocinétiques;

- under the final section, now called **Bioequivalence Requirements for Oral Solid Dosage Forms** to encompass variations to first entry dosage forms;

- dans la dernière section, maintenant intitulée **Exigences de bioéquivalence pour les formes posologiques solides orales**, dont le but est de tenir compte des variations par rapport aux premières formes posologiques mises sur le marché;

- clarifying requirements in the assessment of comparative bioavailability data;

- clarification des exigences dans l'évaluation des données de biodisponibilité comparative;

- revising statements to indicate that bioequivalence criteria "must" rather than "may have to" be met for each enantiomer for conventional oral solid dosage forms where rate of release/absorption affects the *in vivo* enantiomeric ratio and in most instances for modified release products; and

- révision de la formulation quant aux critères de bioéquivalence : ces critères « doivent » « et non pas peuvent » être satisfaits pour chaque énantiomère dans les cas des formes posologiques solides orales classiques quand le taux de libération/absorption influence le ratio des énantiomères *in vivo* et dans le cas de la plupart des produits à libération modifiée; et

- specifying the need to use an enantioselective assay in the case of single enantiomers where *in vivo* inversion

- précision de la nécessité d'utiliser un essai énantiosélectif dans le cas d'un seul énantiomère lorsqu'il

of the enantiomer is known to occur.

est notoire qu'une inversion de l'énantiomère se produit *in vivo*.

Given the extent of revision, this guideline is being circulated a second time for comment. Please direct comments to Dr. Ukken Cheriyan, Division of Pharmaceutical Quality, Bureau of Pharmaceutical Assessment, 11 Holland Avenue, Tower A, 2nd floor, Ottawa, Ontario, K1A 1B6, telephone (613) 957-8151, fax (613) 941-0571 by September 15, 1998.

Étant donné l'ampleur de la révision, nous vous envoyons à nouveau la directive pour obtenir vos commentaires. Veuillez adressez vos commentaires, d'ici le 15 septembre 1998, au Dr. Ukken Cheriyan, à la Division de la qualité des produits pharmaceutiques, Bureau de l'évaluation des produits pharmaceutiques, 11, avenue Holland, tour A, 2e étage, Ottawa (Ontario), K1A 1B6, téléphone : (613) 957-8151, fax : (613) 941-0571.

Original signed by / Original signé par

Dann M. Michols
Director General / Directeur général

Attachment Pièce jointe